UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/769,420 | 01/26/2001 | Sui Xiong Cai | 1735.0440001/RWE/BEC | 4240 |

26111 7590 09/23/2002

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

| EXAMINER |
|---|
| MCKENZIE, THOMAS C |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | 9 |

DATE MAILED: 09/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/769,420 | CAI ET AL. | |
| | Examiner | Art Unit | |
| | Thomas McKenzie Ph.D. | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *33-43,45-47,49-61 and 71-77* is/are pending in the application.

4a) Of the above claim(s) *49,50,72 and 73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-43,45-47,51-58,60,71 and 74-77* is/are rejected.

7)☒ Claim(s) *59 and 61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This action is in response to amendments filed on 7/11/02. Applicant amended claims 33-35, 42, 43, 46, 47, 53-57, 58, and 71. Applicants cancelled claims 1-32, 44, 48, and 62-70. Applicants' new claims 72-75 have been renumbered 74-77 as per rule 126. There are thirty-four claims pending and thirty under consideration. Claims 58-61, 76, and 77 are compound claims. Claim 71 is a composition claim. Claims 33-43, 45-47, 53-57, 74, and 75 are use claims. This is the second action on the merits. The application concerns some nicotinamide compounds, compositions, and uses thereof.

### *Election/Restrictions*

2. Applicant's election without traverse of Group I in Paper No. 7 is acknowledged. The Examiner mistakenly indicated that claims 51 and 52 were withdrawn from consideration. In fact, as indicated in point #2 of the previous action, theses are linking claims. Claims 49 and 50 are drawn to non-elected Group V and correctly withdrawn from consideration in point #4. The Office Action Summary (PTO-326) erroneously indicated that claims 49 and 52 were withdrawn from consideration. Points #2, point #4, and the Office Action Summary all correctly indicated that claims 72 and 73 were withdrawn from consideration.

3. Claims 49, 50, 72, and 73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

***Response to Amendment***

4. Applicants claim cancellations and amendments overcome the improper Markush rejection made in point #6 of the previous office action. Applicants have cancelled all claims containing the limitation "Ar". Applicants point to page 19 as indicating what substituents they intend on the various radicals R. This is persuasive and the indefiniteness rejection made in point #9 is withdrawn. Applicants' point to Nipedipine as a nitro group-containing compound widely used as a drug. This is most persuasive and the enablement rejection made in point #11 is withdrawn. The cancellation of claims containing the radical "Ar' and the amendments discussed above overcome the enablement rejection made in point #12.

Claim 45 was mistakenly included in this blanket rejection in the previous office action. Claim 45 lists the specific cancers to be treated. Thus, the enablement rejection made to this claim in point #13 is withdrawn. Applicants' deletion of "preventing" from claims 42, 43, 46, 47, 51, and 52 overcomes the enablement rejection made in point #14. Applicants' restriction of their use claims

to anilide compound, i.e. compounds which have benzene attached to the amide nitrogen atom overcomes the anticipation rejection made in points #20, and #21, of the previous office action. Applicants' limitation that the fused ring formed by $R_1$ and $R_2$ effectively may not be a heteroaryl ring overcomes the anticipation rejection made in points #22 and #24. Applicants' argument that the compound disclosed in Beeley ('827) is a benzamide not a nicotinamide is persuasive. It is Example 7, not compound 16 as described by Applicants but was incorrectly indexed by Chemical Abstracts. Thus, the anticipation rejection made in point #26 is withdrawn.

***Claim Rejections - 35 USC § 112***

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 33-41 remain rejected and claim 74 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "a disorder responsive to the induction of apoptosis" and "a mammal in need of such treatment" are indefinite. The claims provide for the use of the compounds of formula III, but the claims do not set forth any steps involved in determining how to identify what disorders or mammals are to be treated. It is unclear what diseases and treatments applicant is intending to encompass. A claim is indefinite where it merely recites a use without

any active, positive steps delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Applicants point to O'Reilly, Orrenius, and to the passage spanning line 17, page 22 to line 15, page 24, the passage spanning line 1, page 26 to line 2, page 29, line 24, page 29 to line 2, page 30, and lines 13-16, page 30 as indicative that this is an art-recognized phrase. This is not persuasive.

The artisan using Applicants' invention is a physician, board certified in family practice. O'Reilly's audience are research immunologist, not the practicing physicians who would use Applicants compounds to treat human disease. O-Reilly does not report any clinical data fro any compounds and restricts his discussion to autoimmune diseases. He discusses some diseases for which apoptosis contributes but does not clarify which, if any of these, respond to induction of apoptosis. Orrenius adds cancer and AIDS to the list but again fails to clarify if any of these diseases respond to the induction of apoptosis. The paragraph spanning pages 23 and 24 lists an impressive number of diseases to be treated with Applicants compounds but uses open language. What other diseases are included? Four

diseases are discussed in page 27, EAT, EAE, arthritis, and psoriasis. These are not mentioned by the references cited or by the earlier passage. Are they included in the list or not? There is not a consistent list of which diseases respond to such induction. The material on pages 29 and 30 concerns pharmaceutical compositions. The relevance of this to the meaning of the phrases under discussion is not apparent to the Examiner.

Applicants also argue that Applicants teach how to administer their compounds and this constitutes the positive step of how to use them. The rejection concerns to whom they are to be administer and how the patients are to be selected. Determining whether a given disease responds or does not respond to such an inducer of apoptosis and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. Suppose that a given drug, which has induction properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given

drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time-release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inducers must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inducers of apoptosis *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property that the second drug is capable. It is common for a drug, particularly in the CNS, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some very different drug. There are for example, agents in antiviral and anticancer chemotherapy that are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

6. Claims 33-38, 40, 42, 43, 45-47, 51-58, 60, and 71 remain rejected and claims 74-77 newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "prodrug", which occurs in claims 33, 40, 42, 43, 46, 47, 58, 60, 74, and 77 is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

Applicant point to the paragraph spanning pages 21 to 22 as indicative of the structures of the prodrugs they intend. This is not completely persuasive for four reasons. Firstly, the passage uses open language, "examples" "e.g.". Secondly, claim 77 concerns the esters, imines, carbamates, and ketals described in the passage. Presumably, claims 33, 42, 46, 58, and 74 upon which claim 77 depends

are broader. What other prodrugs are claimed in claims 33, 42, 46, and 58 and are not the ones described in the passage cited? Thirdly, claim 77 recites "esters of a hydroxyl group". Are these esters limited to the $C_{1-4}$ carboxylic acids etc listed in lines 27-29? Alternatively, are other acids also included in this phrase? Similar questions occur with the other claims imines, carbamates, and ketals. Fourthly, the claims measure the invention. The U.S. Court of Customs and Patent Appeals wrote *In re Priest*, 199 USPQ 11 "We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim." *In re Prater*, 56 CCPA 1381, 1396, 415 F.2d 1393, 1405, 162 USPQ 541, 551 (1969)." The Examiner suggests adding the

The Examiner suggests using the passage cited to claim the specific "prodrugs" they intend.

7. Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are two grounds of rejection. Firstly, this is a compound claim, yet it is dependant upon use claims 33, 42, 46, and 74. Secondly, do the substituted aryl and heteroaryl groups refer to the

benzene and pyridine ring of Formula (III)? On the other hand, does this apply only to the aromatic rings of Groups $R_{11}$, $R_{15}$, and $R_{16}$?

8. Claims 33-41 remain rejected and claim 74 is newly under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The how to use portion of the statute means that Applicants must teach the skilled practitioner, in this case a physician, how to treat the claimed disease. The physician clearly must know what disease and what symptoms she is to treat.

The factors to be considered in an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, and the predictability or unpredictability of the art. *Ex parte Formal*, et al., 230 USPQ 546. The issue of which diseases are covered by this claim are discussed above.

The artisan using Applicants' invention to treat human disease is a general practitioner with a MD degree. The experimentation required would be a double blind clinical trial and as discussed is potentially inconclusive. The guidance concerning the diseases to be treated is also discussed above. The invention

concerns human disease treatment, which is inherently unpredictable. Applicants have not asserted and it is not clear to the Examiner that any compound that induces apoptosis as its only mechanism of action has ever shown clinical efficacy toward any human disease. The passage spanning pages 27-29 describes Fas-ligand, psoralen, CD2, and Bcl-2. It is not clear to the Examiner the relevance of this to Applicants' claim limitation. Thus, there can be no predictability in the art of disease treatment with such compounds.

9. Claims 42, 43, 46, 47, 51, and 52 remain rejected and claims 76 and 77 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants are not enabled for "treating or preventing cancer" generally. There are two issues here. Firstly, Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

Applicants cite Ruddon, WO 00/04901, and Los in support of their contention that cancer generally may be treated by inducers of apoptosis. This is not persuasive for three reasons. Firstly, the case law referred to above makes such

a claim inherently suspect. Secondly, none of the references cited contain any clinical data concerning the treatment of any cancer, let alone cancer generally.

Thirdly, in the art of clinical oncology, no compound has yet shown clinical efficacy against every type of cancer. To quote Salmon (Principles of Cancer Therapy) in the paragraph on page 1038 titled Medical Therapy "Curative therapy has been developed for a series of relatively uncommon neoplasms and useful palliative therapy has been developed for some common forms of cancer (Table 162-4). With rare exceptions, effective therapy has utilized combinations of anticancer drugs." Applicant's attention is drawn to Tables 162-6, 162-7, 162-8, 162-162-9, 162-10, and the material on pages 1045-1046 titled Miscellaneous Anticancer Agents in Salmon (Principles of Cancer Therapy). Different agents are used for different specific forms of cancer and no single agent is listed as a treatment of every single type of cancer. To quote Balasubramanian (Recent Developments in Cancer Cytotoxics) from page 151 first paragraph "[t]he successful treatment of solid tumors remains a formidable challenge. The partial success of traditional cancer chemotherapy...". On page 158, second paragraph Balasubramanian (Recent Developments in Cancer Cytotoxics) states: "The future scenario in clinical management of cancer will be mainly dictated by the availability of less toxic and tumor selective agents". No compound has shown

clinical efficacy against all cancers, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. Applicants' specification logically must lack such assay data.

10. Claim 53 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The treatment of "autoimmune diseases" generally would be unprecedented feat. For a compound or genus to be effective against "autoimmune diseases" generally is contrary to medical science. The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds of such diseases, which have fundamentally different mechanisms and different underlying causes. There are both chromic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented

in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Applicants cite O'Reilly and point to lines 7-31, page 26 as providing support for the claims. This is not persuasive for three reasons. Firstly, neither O'Reilly nor the papers in the passage cite any clinical data for the treatment of any human disease. Secondly, no compound has shown clinical efficacy against all autoimmune diseases, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. Applicants' specification logically must lack such assay data.

Thirdly, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myesthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE)

antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once an patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it.

This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such differing mechanisms, it is not logical that a cure for autoimmune diseases generally can be found.

11. Claim 56 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of "skin disease" cannot be deemed enabled. The term "skin disease" covers a broad array of

different disorders that have different modes of action and different origins. The term would embrace such unrelated disorders as sun burn, acne, and melanoma. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609.

12. Applicants argue that treatment of psoriasis is enabled by the paragraph spanning pages 27 to 28 and Ozawa. This is true but not relevant. The rejection concerns all skin diseases generally, not one specific skin disease.

13. Claims 33-38, 40, 42, 43, 45-47, 51-58, 60, 71, and 75-77 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The provisos in the last ten lines of claims 33, 42, 46, the last three lines of claim 34, and the last two lines of claim 58 of claim 17 lack description. Nowhere in the specification is such a relationship linking the description among radicals $R^1$ through $R^{11}$ described. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the

specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts."

14. Claims 74, 76, and 77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The proviso in the last two lines of claim 74 lacks description. Nowhere in the specification is the concept that the three diseases not responsive to apoptosis present. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393. There are two reasons for making this rejection. Firstly, since the phrase "a disorder responsive to the induction of apoptosis" is indefinite, Applicants may be excluding species not present in the genus. Secondly, the clearest indication as what diseases Applicants intend to treat is in the paragraph spanning page 23 to 24. The three diseases do not occur in the list. The diseases are listed in the passage spanning pages 26-29 but it is not clear to the Examiner that theses are diseases Applicants intended to treat with his compounds.

***Claim Rejections - 35 USC § 102***

15. Claim 58 remains rejected under 35 U.S.C. 102(b) as being anticipated by Setliff (Proc. Arkansas Acad. Sci.) for reasons cited in the previous action. A complete copy of this reference has been ordered.

16. Claims 58 and 71 remain rejected under 35 U.S.C. 102(b) as being anticipated by Yagihara ('385) for reasons cited in the previous action.

17. Claims 33, 34, 36, 38, 74, and 75 are newly rejected and claims 42, 45, 46, 53, 54, 56, and 57 remain rejected under 35 U.S.C. 102(b) as being anticipated by Gammill ('075). Compound 16 of the reference anticipates Applicants' use claims and fits formula (III) with $R_6 = R_7 = R_9 = R_{10}$ = hydrogen, $R_1 = R_4 = R_5$ = hydrogen, and $R_2 = R_3$ = 4-morpholinyl)-4H-benzopyran-4-on-6-yl. The compound is found in lines 54-55, column 20. Activity against cancer, arthritis, and psoriasis is disclosed in in lines 11-24, column 16.

18. Claims 33, 36, 38, 53, and 54 remain rejected and claims 74 and 75 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Kubotab (WO 99/19303 A1). There is one compound in this reference, which anticipates Applicants' use claims. It is entry 36 on page 36. It and fits formula (III) with $R_6 = R_7 = R_9 = R_{10}$ = hydrogen, $R_1 = R_2 = R_4 = R_5$ = hydrogen, and $R_3$ = 3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl. Activity against autoimmune diseases and rheumatoid arthritis is taught in the abstract. Rheumatoid arthritis is an inflammatory disease not

specifically excluded by claim 74. Thus, both claims 74 and 75 are anticipated. An English traslation of this referencehas been ordered.

19. Claims 33, 53, and 54 remain rejected and claims 38, 74, and 75 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Clemence ('140). There is one compound in this reference, which anticipates Applicants' use claims. The compound was cited previously and fits formula (III) with $R_6$ = hydroxy, $R_7$ = trifluoromethyl, $R_9 = R_{10}$ = phenyl and $R_1 = R_2 = R_3 = R_4 = R_5$ = hydrogen. It is Example 4, lines 13, column 10 to line 43, column 11. Activity against rheumatoid arthritis is taught in claim 15 of the reference. Rheumatoid arthritis is an inflammatory disease and not specifically excluded by claim 74. Thus, both claims 74 and 75 are anticipated.

20. Claims 33, 36, 42, 45, 46, and 53-57 remain rejected and claims 38, 74, and 75 newly rejected under 35 U.S.C. 102(e) as being anticipated by Mantlo ('884). There are over one hundred compounds disclosed in this reference, which anticipate Applicants' use claims. One compound was previously cited and fits formula (III) with $R_6 = R_7 = R_{10}$ = hydrogen, $R_9$ = phenylamino, $R_1 = R_2 = R_4 = R_5$ = hydrogen, and $R_3$ = methoxy. The compounds are found in Tables 8-13, spanning columns 84-91. See also compound claims 1-15 in this reference. Activity against rheumatoid arthritis is taught in line 36, column 96 of the

reference. Activity against inflammatory bowel disease and psoriasis is taught in line 40-41, column 96. Activity against cancer is taught in line 57, column 96.

Applicants' new provisos referred to above, exclude anticipatory compounds. However, the provisos are new matter and the anticipation rejections are maintained.

***Allowable Subject Matter***

21. Claims 59 and 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In

no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
September 19, 2002